UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/342,024 | 06/28/1999 | PETERS JR., GERALD G. | | |

Lisa A. Haile, J.D. Ph.D.
GRAY CARY WARE & FREIDENRICH LLP
4365 Executive Drive
Suite 1100
San Diego, CA 92121-2133

PETERS JR, GERALD G

| ART UNIT | PAPER NUMBER |
|---|---|
| 1636 | |

22

Please find below and or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/342,024 | NOLAN ET AL. | |
| | Examiner | Art Unit | |
| | Gerald G Leffers Jr. | 1636 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *04 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,5,7-12,17,19-22 and 30-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,7-12,17,19-22 and 30-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

Receipt is acknowledged of an amendment, filed 3/4/03 as Paper No. 20. In Paper No. 20 several claims were cancelled (claims 2-4, 13-16, 18 and 23-29) and claims were amended (claims 1 & 39). This amendment does not introduce new issues and has been entered into the file. Also received was a 37 C.F.R. §1.132 Declaration filed by Dr. Dietmar P. Rabussay (Paper No. 21 filed 3/4/03). The declaration has been considered in full.

Applicant's are hereby notified that prosecution of the instant application is REOPENED for reasons outlined below. Any rejection of record for the instant application that is not addressed in the instant action has been withdrawn. Claims 1, 5, 7-12, 19-22, 30-39 are pending in the instant application and are under consideration. This is not a final action.

### *Response to Amendment*

The major issue remaining in the instant application is whether the Dev et al patent (U.S. Patent No. 5,944,710) anticipates the claimed invention. The examiner has asserted in previous actions that the teachings of Dev et al anticipate the recited limitation of a combination of 300-600 V/cm and 10-100 milliseconds for the claimed electroporation methods. Applicants have responded that the Dev et al patent doesn't actually teach the ***combination*** of the recited ranges and does not exemplify an embodiment wherein nucleic acids are electroporated *in vivo* using parameters that fall within the combination of the two recited ranges. In Paper No. 20, applicants have further argued that the Dev et al patent is not available as prior art due to the amendments to 35 U.S.C. §102(e) under H.R. 2215 (Technical Amendment Act) and in light of

the §1.132 Declaration by Dr. Rabusssay that the present application and the Dev et al patent are commonly owned. MPEP 706.02(l)(1) states the following:

> For applications filed **prior to November 29, 1999**, the subject matter that is disqualified as prior art under 35 U.S.C. 103(c) is strictly limited to subject matter that A) qualifies as prior art only under 35 U.S.C. 102(f) or 35 U.S.C. 102(g), and B) was commonly owned with the claimed invention at the time the invention was made. If the subject matter that qualifies as prior art only under 35 U.S.C. 102(f) or 35 U.S.C. 102(g) was not commonly owned at the time of the invention, the subject matter is not disqualified as prior art under 35 U.S.C. 103(c). See OddzOn Products, Inc. v. Just Toys, Inc., 122 F.3d 1396, 1403-04, 43 USPQ2d 1641, 1646 (Fed. Cir. 1997) ("We therefore hold that subject matter derived from another not only is itself unpatentable to the party who derived it under § 102(f), but, when combined with other prior art, may make a resulting obvious invention unpatentable to that party under a combination of §§ 102(f) and 103.") If the subject matter qualifies as prior art under any other subsection (e.g., subsection 35 U.S.C. 102(a), 35 U.S.C. 102(b), or 35 U.S.C. 102(e)) it will not be disqualified as prior art under 35 U.S.C. 103(c).
>
> It is important to recognize that 35 U.S.C. 103(c) applies only to consideration of prior art for purposes of obviousness under 35 U.S.C. 103. **It does not apply to or affect subject matter which qualifies as prior art under 35 U.S.C. 102.** (emphasis added by the examiner)
>
> **The term "commonly owned" means wholly owned by the same person(s), or organization(s) at the time the invention was made. See MPEP § 706.02(l)(2).** (examiner's emphasis added)

The instant application was filed prior to November 29, 1999. The H.R. 2215 changes to §102(e) thus do not apply here. As stated above, 35 U.S.C. §103(c) does not apply to rejections for anticipation for applications filed prior to November 29, 1999. In addition, the Dev et al patent qualifies as prior art under §102(e) (i.e. date wise), so that even if the rejection was for obviousness under 35 U.S.C. §103, a showing of common ownership would not obviate the rejection. Finally, the declaration by Dr. Rabussay does not make clear that both applications were "wholly owned" as defined above. Specifically, although Dr. Rabussay states that Genetronics Inc. is the Assignee of 100 percent interest in each application at the moment, he further states that Genetronics Inc. was the "co-owner" of the subject matter of each application

at the time of the respective inventions. Thus, it is confusing as to whether Genetronics Inc. wholly owned both inventions at the time the instant invention was made. ***Clarification on this point is requested.*** For at least these reasons, applicant's arguments presented in Paper No. 20 are not persuasive regarding the rejection made under 35 U.S.C. §102(e) for anticipation by the teachings of the Dev et al patent.

However, upon further review and consideration of applicants' arguments presented in Papers No. 12 and 19, the first §1.132 Declaration by Dr. Rabusssay (Paper No. 19), the instant specification and the Dev et al patent, the examiner finds persuasive the argument that Dev et al does not explicitly teach the particular ***combination*** of ranges recited in the instant claims. Accordingly, the rejection of the instant claims as anticipated by the Dev et al patent is hereby withdrawn. A rejection of the instant claims as being obvious over the teachings of Dev et al follows.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 5, 7-12, 19-22, 30-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dev et al (U.S. Patent No. 5,944,710; see the entire reference). **This is a new rejection.**

The Dev et al patent (the '710 patent) teaches compositions and methods for the sustained intravascular delivery via electroporation of therapeutic compositions (Abstract). The therapeutic compositions of the invention include nucleic acids such as plasmids or anti-sense oligonucleotides against c-myc or c-myb (column 3, line 21; column 5, lines 15-21). The electric fields needed for in vivo cell electroporation according to the invention can range from 100V/cm to several kV/cm (column 10, lines 1-9). The waveforms of the voltage pulse provided by the generator in the power pack can be exponentially decaying pulse, square pulse, unipolar oscillating pulse train or bipolar oscillating pulse train (column 10, lines 55-60) The pulse length can be 100 microseconds to 100 milliseconds, preferably from about 500 microseconds to 10 milliseconds. From about 1 to 10 pulses can be applied to an area or group of cells (column 11, lines 5-10). A gene transfer experiment is exemplified wherein a standard marker gene, lacZ driven by a CMV promoter, was injected into an artery followed by electroporation (three pulses at 10 second intervals at 76 V and .76 milliseconds) (column 14, lines 15-49). The '710 patent teaches that the composition comprising DNA can be administered by gradual perfusion, intravenously, intraperitoneally, intramuscularly, subcutaneously, intracavity, transdermally or intravascularly near the site of electroporation (column 6, lines 19-24).

Dev et al do not explicitly teach the selection of a combination of electroporation parameters comprising 300-600 V/cm and 10-1000 milliseconds for the electroporation of nucleic acids *in vivo*.

Dev et al do teach an example directed towards further drug delivery studies wherein the electroporation parameters used fall within those recited in the rejected claims. In Example 3, Dev et al teach electroporation into New Zealand white rabbits using parameters of 200-300 V/cm (i.e. 60 V/2-3 millimeter gap) and four pulses at 1 Hz each of 40 milliseconds (e.g. columns 14-15, bridging paragraphs).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the conditions taught by Dev et al for the electroporation of nucleic acids in vivo to include the suggested parameters for further electroporation studies (e.g. 200-300 V/cm and 40 millisecond pulses) because Dev et al teach it is within the skill of the art to use electroporation parameters with the broad ranges of 100 V/cm-several kV/cm and 100 microseconds-100 milliseconds, and because Dev et al teach it is within the skill of the art to further optimize the conditions for drug delivery to include parameters of ~200-300 V/cm and ~ 40 milliseconds/pulse. One of ordinary skill in the art would recognize that Dev et al consider nucleic acids to be potential drugs for delivery by their electroporation methods. One would have been motivated to do so in order to optimize delivery conditions, as suggested by Dev et al. Absent any evidence to the contrary, there would have been a reasonable expectation of success in practicing the claimed invention using the optimization conditions suggested by Dev et al (e.g. ~200-300 V/cm and ~ 40 milliseconds/pulse).

It is noted that applicants can overcome the instant rejection by refiling the instant application as a CPA application in order to place the claims under the changes to 35 U.S.C. §102(e) made by H.R. 2215 (Technical Amendment Act). MPEP 706.02(l)(1) states:

> **706.02(l)(1) Rejections Under 35 U.S.C. 102(e)/103; 35 U.S.C. 103(c)**
> ***35 U.S.C. 103. Conditions for patentability; non-obvious subject matter.***
> ***(c) Subject matter developed by another person, which qualifies as prior art only under one or more of subsections (e), (f), and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.***
>
> Effective November 29, 1999, subject matter which was prior art under former 35 U.S.C. 103 via 35 U.S.C. 102(e) is now disqualified as prior art against the claimed invention if that subject matter and the claimed invention "were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person." This change to 35 U.S.C. 103(c) applies to all utility, design and plant patent applications filed on or after November 29, 1999, including continuing applications filed under 37 CFR 1.53(b), continued prosecution application filed under 37 CFR 1.53(d), and reissues. The amendment to 35 U.S.C. 103(c) does not affect any application filed before November 29, 1999, a request for examination under 37 CFR 1.129 of such an application, nor a request for continued examination under 37 CFR 1.114 of such an application. **The mere filing of a continuing application on or after November 29, 1999, with the required evidence of common ownership, will serve to exclude commonly owned 35 U.S.C. 102(e) prior art that was applied, or could have been applied, in a rejection under 35 U.S.C. 103 in the parent application.** (examiner's emphasis added)

Such a filing would necessarily require clarification that the inventions were wholly owned by the Genetronics Inc. at the time of the instant invention (e.g. see above under Response to Amendments).

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 39 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction of guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary. Each of the factors has been fully considered, with the most relevant elements outlined below.

Claim 39 is drawn towards a method for electroporation of nucleic acids into the cells of a subject wherein the nucleic acid encodes a "therapeutic" protein. The claims encompass any subject, including a human. The limitation of encoding a therapeutic protein combined with the broad scope of the invention with regard to the subject cause the rejected claim to read on the highly complex art of gene therapy for a human subject.

An analysis of the prior art as of the effective filing date of the present application shows the complete lack of documented success for any treatment based on gene therapy. In a review on the current status of gene therapy, both Verma et al (Nature (1997) 389:239-242) and Palù et

al (J. Biotechnol. (1999) 68: 1-13) state that despite hundreds of clinical trials underway, no successful outcome has been achieved. See Verma et al, p. 239, 1st paragraph; Palù et al, p. 1, Abstract. The continued, major obstacles to successful gene therapy are gene delivery and sustained expression of the gene. Regarding non-viral methods for gene delivery, Verma et al indicates that most approaches suffer from poor efficiency and transient expression of the gene (p. 239, col. 3, 2nd paragraph). Likewise, Luo et al (Nature Biotechnology (2000) 18:33-37) indicates that non-viral synthetic delivery systems are very inefficient. See p. 33, Abstract and col. 1, 1st and 2nd paragraphs. While all three references indicate the promise of gene therapy, it is still a technique of the future and advancements in our understanding of the basics of gene delivery and expression must be made before gene therapy becomes a useful technique. See Verma et al, p. 242, col. 2-3; Palù et al, pp. 10-11; Luo et al , p. 33, col. 1, 1st paragraph.

The area of the invention is unpredictable. As discussed above, the method of in vivo or ex vivo gene therapy is highly complex and unpredictable. The skilled artisan at the time the present invention was made recognized the difficulty of achieving sufficient heterologous gene expression to induce any therapeutic effect.

The quantity of experimentation necessary to carry out the claimed invention is high as the skilled artisan could not rely on the prior art or the present specification to teach how to use the claimed methods. In order to determine how to use the method to treat a condition, one of skill in the art would have to determine what effect exogenous transgene expression would have in any cell type, whether the effect could be exploited for treatment of a disease, how to deliver the given nucleic acid to the appropriate target cells with specificity and efficiency, and how to get sufficient expression to induce at least some therapeutic effect. Since neither the prior art nor

the specification provides the answers to all of these questions, it would require a large quantity of trial and error experimentation by the skilled artisan to do so.

Based on the broad scope of the claims, the unpredictability in the area of the invention, the lack of sufficient guidance or working examples in the specification and the quantity of experimentation necessary, it would clearly require undue experimentation by one of skill in the art to determine how to practice the claimed method to achieve a therapeutic result.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 5, 8-12, 34 are rejected under 35 U.S.C. 102(a) as being anticipated by Suzuki et al (FEBS Letters, 3 April 1998, Vol. 425, No. 3, pages 436-440; see the entire document).

Suzuki et al teach electroporation methods for the direct transfer of nucleic acids to rat liver cells *in vivo* (e.g. Abstract; Figure 1). The conditions taught by Suzuki et al include voltages of 25, 50 and 100 Volts for durations of 25, 50 and 99 milliseconds across a field distance of .2 centimeters (i.e. field strengths of 125 V/cm to 500 V/cm) (see e.g. pages 436-437, bridging paragraph; Figures 4-5, column 6; page 438, columns 1-2). The nucleic acid used in the experiments taught by Suzuki et al encoded the green flourescence protein (GFP) marker (see e.g. page 436, column 2, paragraph 2.1).

***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr. whose telephone number is (703) 308-6232. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-7939 for regular communications and (703) 305-7939 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gerald G Leffers Jr.
Examiner
Art Unit 1636

Ggl
March 27, 2003